

Review Article

$\gamma\delta$ T Cells and the Extracellular Matrix: An Unmapped Sensing Axis in Barrier Immunity, Neuroinflammation and Cancer

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$\gamma\delta$ T cells, a tissue-resident lymphocyte lineage recognizing antigen independently of major histocompatibility complex, are examined for their largely unaddressed capacity to sense and respond to the extracellular matrix (ECM) across ECM-rich barrier tissues where they disproportionately reside. Extending an outside-in/inside-out mechanotransduction framework built almost entirely from conventional $\alpha\beta$ T cells, macrophages, and stromal cells, a dedicated $\gamma\delta$ T cell ECM-sensing mechanism is argued to represent a substantial gap in barrier immunity. In $\alpha\beta$ T cells, this framework has recently been resolved at the molecular level: integrin engagement with a stiff ECM drives actin polymerization, nuclear deformation, and YAP nuclear translocation, culminating in IL-2-dependent activation independently of the T cell receptor. Whether this integrin-actin-YAP axis, or any equivalent, operates in $\gamma\delta$ T cells has not been tested, despite their expression of the ECM-binding integrins CD103 and CD49a, with tissue-resident subsets such as V δ 1 positioned as plausible candidates given their long-term anatomical commitment to ECM-rich niches in gut, skin, and epithelial barriers. $\gamma\delta$ T cell roles in neuroinflammation, including basement-membrane crossing at the blood-brain barrier and microglial activation, and in the tumour microenvironment, where a stiffened, glycan-altered collagen matrix limits solid-tumour infiltration despite strong cytotoxicity against cancer cells, are reviewed as settings where ECM mechanosensing may govern $\gamma\delta$ T cell function, with implications for engineering ECM-penetrant $\gamma\delta$ T cell cancer immunotherapies.

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Introduction

The extracellular matrix (ECM) is essential not only for providing structural support but also for conveying information to cells. Stoker and colleagues first demonstrated this in 1968, showing that cell adhesion to a rigid surface is necessary to complete mitosis. This finding established that the ECM does not merely support replication, but also directs growth, differentiation, and apoptosis. As cells attach to the ECM, they form focal adhesions, the junctions that link the cytoskeleton to the extracellular space. These links are central to mechanotransduction, the process by which physical and mechanical signals are converted into biochemical signals that direct cellular behaviour.

This raises a significant question: given that tissue stiffness varies enormously, from soft tissues such as brain and lung to rigid bone, how do cells calibrate their response to match the specific mechanical demands of their local environment? This calibration depends on a balance between two signalling directions: outside-in signalling, in which the ECM directs cell behaviour, and inside-out signalling, in which cells actively remodel the ECM around them. Both directions rely on functioning mechanotransduction to remain in balance. When this bidirectional signalling is disrupted by ageing or disease, ECM turnover becomes dysregulated, with pathological consequences. In cancer, tumour cells signal to fibroblasts to stiffen the surrounding stroma, a process that promotes invasion. In cardiac injury, a similar loss of balance drives fibroblasts to overproduce ECM, resulting in cardiac fibrosis^[1].

The ECM itself has emerged as a dynamic, physiologically active component of the immune landscape rather than an inert scaffold. It is composed of fibrillar proteins such as collagen and fibronectin, glycosaminoglycans, proteoglycans, and mucus, which together create a microenvironment that profoundly shapes immune cell behaviour. The ECM physically guides immune cell movement and positioning, and heparan sulfate proteoglycans within tissues bind and present chemokines to form the directional gradients that leukocytes follow. ECM composition and stiffness are increasingly understood to be sensed through dedicated mechanosensing machinery, including mechanosensitive ion channels such as Piezo1, so that the matrix regulates immune cell survival, mobility and function through bidirectional signalling that mirrors the cell-ECM relationship described above^[2]. Almost the entirety of this mechanistic picture, however, has been built from work on conventional $\alpha\beta$ T cells, macrophages, and stromal cells. Whether $\gamma\delta$ T cells, a lymphocyte lineage that resides disproportionately within the ECM-rich barrier tissues of the body, sense and respond to the matrix in the same way remains an open and largely unaddressed question. This paper reviews what is known about $\gamma\delta$ T cell biology and their

documented physical relationships with the ECM, and argues that the specific sensing mechanisms which convert ECM contact into $\gamma\delta$ T cell behaviour represent a substantial and clinically relevant gap in the literature.

$\gamma\delta$ T cells were first identified in 1984, distinguished from conventional $\alpha\beta$ T cells by their use of γ and δ chains instead of α and β chains in the T cell receptor. $\alpha\beta$ T cells recognise peptide antigens only in the presence of major histocompatibility complex (MHC) molecules, whereas $\gamma\delta$ T cells can recognise antigens independently of MHC, including stress-induced molecules and non-peptide antigens that $\alpha\beta$ T cells cannot detect. This structural difference plays a major role in shaping their distinct functions. Activation mechanisms also differ: $\gamma\delta$ T cells can be activated by a single signal, while $\alpha\beta$ T cells require two signals, antigen recognition plus co-stimulation. This equips $\gamma\delta$ T cells with features of both innate and adaptive immunity, allowing them to respond faster and without prior antigen exposure^[3].

$\gamma\delta$ T cells make up only about 1–5% of circulating T cells in peripheral blood but are present at much higher proportions in specific tissues, reaching nearly 40% of intraepithelial lymphocytes in the intestine and 10–30% of T cells in the skin. Alongside this tissue enrichment, $\gamma\delta$ T cells are actively involved in tissue surveillance at barrier sites, contributing to tissue homeostasis^[3]. It is precisely this tissue distribution, concentrated at interfaces where the ECM is most abundant, most mechanically diverse, and most frequently remodelled by injury and infection, that makes the absence of a dedicated account of $\gamma\delta$ T cell ECM sensing so conspicuous.

This tissue enrichment is not distributed evenly across a single, uniform $\gamma\delta$ population but reflects a small number of subsets defined by their γ - and δ -chain variable region usage. In human peripheral blood, the dominant subset is V γ 9V δ 2, which recognises phosphoantigens in an MHC-independent manner and is the subset most commonly exploited in current cellular immunotherapy programmes, whereas V δ 1 cells are comparatively rare in blood but dominate the tissue-resident compartment described above, in the gut, skin and other epithelial barriers^[3]. In mice, the equivalent tissue-resident populations are organised by γ -chain usage and by the developmental wave in which they seed a given tissue, with the epidermis populated almost exclusively by a single invariant subset, discussed further below, and the gut and other tissues populated by distinct, more heterogeneous waves of $\gamma\delta$ T cells. This subset structure matters for the argument developed in this review because it means that any ECM-sensing mechanism, if one exists, need not be uniform across the $\gamma\delta$ lineage: a tissue-resident subset such as V δ 1, which is anatomically committed to an ECM-rich niche for the long term, is a priori a more

plausible candidate for a dedicated mechanotransduction pathway than a circulating subset such as V γ 9V δ 2, which encounters the ECM only transiently.

$\gamma\delta$ T cells and the extracellular matrix: adhesion, mechanics and a missing mechanism

Both $\alpha\beta$ and $\gamma\delta$ T cells rely on integrin-mediated adhesion for navigating tissue barriers, but the two lineages have not been studied with anything like the same rigour when it comes to how these integrins translate matrix contact into a functional response. T cell interactions with the ECM are mediated through integrin family adhesion receptors that connect the intracellular actin cytoskeleton to ECM components such as fibronectin, laminin and collagen. Gray and colleagues' study of human $\gamma\delta$ T cells across diverse tissues found that tissue-resident $\gamma\delta$ T cells, specifically the V δ 1 subset, express two surface integrins, CD103 and CD49a, which bind E-cadherin and collagen respectively. Expression of these proteins is higher in the gut and increases with age^[4]. This finding is important for two reasons. First, it confirms that $\gamma\delta$ T cells do not merely sit within ECM-rich tissue but physically grip the matrix and its associated adhesion molecules through the same integrin vocabulary used by other tissue-resident lymphocytes. Second, and more strikingly, it stops short of asking the harder question: whether this adhesion event is silent, or whether it triggers the kind of mechanotransductive signalling cascade that has been mapped in such detail for $\alpha\beta$ T cells. Gray and colleagues describe the receptors; they do not describe what the receptors do once engaged. This is precisely the gap that the remainder of this review returns to repeatedly across different tissue contexts.

The broader immunology literature makes clear that this is not a trivial omission. Sutherland, Dyer and Allen's synthesis of ECM-immune biology shows that the ECM does not simply form a physical barrier but actively shapes how T cells migrate through tissues. T cells prefer to travel through regions with thin, loosely organised collagen and fibronectin fibres, avoiding dense matrices that have been stiffened through cross-linking by enzymes such as lysyl oxidase (LOX). This process is active, not passive: the mechanical properties of ECM fibres, including their capacity to stretch, directly regulate integrin-mediated binding and the biochemical signals that follow. Inflamed skin provides a clear example, where structural changes to fibronectin fibres enhance integrin binding to the point of arresting T cell migration, causing cells to accumulate at perivascular sites rather than moving further into the tissue. This mechanosensing capacity is not restricted to integrins alone; receptors such as Piezo1, a

mechanosensitive ion channel, show that immune cells can respond to physical force more broadly, and transforming growth factor- β (TGF- β) together with type 2 cytokines such as interleukin-13 have been identified as modulators of ECM quantity and quality in their own right. Together, this evidence suggests that ECM mechanics do not merely restrict T cell movement but actively instruct T cell behaviour through integrin-mediated mechanotransduction^[2]. Every one of these observations, from stiffness-avoidance to LOX-dependent arrest to Piezo1 responsiveness, has been generated in mixed T cell populations or in conventional $\alpha\beta$ T cells; none has been tested with $\gamma\delta$ T cells isolated as a distinct population, despite the fact that $\gamma\delta$ T cells are the resident lymphocyte at exactly the barrier sites, skin and gut, that these studies use as their model tissues.

Recent work in $\alpha\beta$ T cells has gone further and characterised a specific integrin-mediated mechanotransduction pathway in molecular detail. Feng and colleagues showed that when $\alpha\beta$ T cells engage a stiff ECM through integrins, F-actin polymerisation takes place as actin filaments bundle together near the cell surface where integrins grip the matrix. The accumulation of actin results in nuclear deformation, and YAP (yes-associated protein), a gene regulator normally present in the cytoplasm, translocates into the nucleus. Once inside, YAP activates transcription, driving IL-2 expression and full T cell activation. Notably, this pathway depends on actin polymerisation rather than myosin contraction, confirmed using the actin polymerisation inhibitor cytochalasin D, which broke the entire chain, while the myosin inhibitor blebbistatin had negligible effect. This distinguishes T cells from most other cell types, which rely on myosin-driven contractile force. Importantly, integrins, rather than the T cell receptor itself, were identified as the dominant mechanical sensor of ECM stiffness in this context^[5].

No equivalent pathway has been characterised in $\gamma\delta$ T cells. This absence is significant given that $\gamma\delta$ T cells reside at disproportionately high proportions in ECM-rich barrier tissues^[3] and already express ECM-binding integrins including CD103 and CD49a^[4]. Whether the same mechanical chain, comprising integrin sensing, actin polymerisation, nuclear deformation, and YAP translocation, operates in $\gamma\delta$ T cells remains untested. This gap has direct translational relevance, as $\gamma\delta$ T cells are currently being developed as cancer immunotherapy agents. Understanding whether they respond to ECM stiffness in the same way as $\alpha\beta$ T cells would inform how to engineer them to infiltrate stiff tumour microenvironments, a point developed further below.

$\gamma\delta$ T cells at barrier tissues: the gut

Intestinal intraepithelial lymphocytes (IELs) are situated at the interface of the intestinal lumen, which is regularly exposed to food and microbes, and the core of the body. Sullivan and colleagues have shown that this positioning is functionally reciprocal rather than one-directional: $\gamma\delta$ T cells regulate the epithelium's transcriptional response to dietary nutrients by suppressing interleukin-22 (IL-22) production from type 3 innate lymphoid cells, and the transcriptome and tissue localisation of $\gamma\delta$ T cells are themselves altered by dietary composition^[6]. This circuit demonstrates that $\gamma\delta$ IELs integrate environmental signals, including nutrient composition, with epithelial remodelling, and it establishes that $\gamma\delta$ T cells are capable of sensing and responding to changes in their local environment with considerable sensitivity. It does not, however, establish whether that sensitivity extends to the physical architecture of the tissue itself, the basement membrane and collagen scaffold against which the epithelium and its resident lymphocytes sit.

The nature of IEL responses to luminal microbes has been studied using high-resolution microscopy and genetic tools with an unusual degree of precision. Hoytema van Konijnenburg and colleagues observed that TCR $\gamma\delta$ IELs display a unique location and movement pattern within the epithelial compartment, one that is directly shaped by the microbiota. Using intravital microscopy in TCR $\gamma\delta$ reporter mice, the authors showed that $\gamma\delta$ IELs migrate almost exclusively in the space between the epithelial layer and the basement membrane, actively patrolling the villus rather than remaining stationary. In naive mice under normal conditions, $\gamma\delta$ IELs were in constant motion, with each cell covering approximately 950 μm^2 of villus surface per hour at a speed of around 6 μm per minute. This movement followed a defined pattern rather than being random. In germ-free mice, this pattern collapsed, with coverage falling substantially and vertical movement between the villus tip and the crypt almost disappearing. When commensal microbiota was reintroduced, the cells resumed patrolling. This indicated that the microbial environment actively signals to $\gamma\delta$ T cells to direct their movement, and that this behaviour is not intrinsic to the cell but instructed by its surroundings.

When mice were infected with *Salmonella* Typhimurium or *Toxoplasma gondii*, $\gamma\delta$ IEL behaviour changed dramatically within two hours. The smooth patrolling pattern gave way to sharp, angled in-and-out movements between adjacent epithelial cells. The cells would move down into the space between two epithelial cells, back up, and across to the next gap, in a motion the authors term flossing. Flossing concentrated at hotspots near the sites of pathogen presence. Using inducible epithelial-cell-specific

Myd88 knockout mice, the authors then showed that this response depended on microbial sensing by the surrounding epithelial cells rather than by the $\gamma\delta$ T cells themselves. Blocking the $\gamma\delta$ TCR did not prevent flossing, confirming that epithelial cells sense the pathogen and signal outward to instruct $\gamma\delta$ IEL behaviour, largely independent of the TCR^[7].

This body of work characterises $\gamma\delta$ IEL behaviour and the epithelial signalling that instructs it in exceptional detail, yet the mechanical properties of the basement membrane along which these cells patrol remain unexamined. Gray and colleagues have already established that gut-resident $\gamma\delta$ T cells express the ECM-binding integrins CD103 and CD49a, meaning the physical machinery for direct ECM engagement is in place^[4]. Whether the integrin-mediated mechanotransduction chain characterised in $\alpha\beta$ T cells by Feng and colleagues also operates here, and whether ECM stiffness or basement-membrane remodelling modulates $\gamma\delta$ IEL motility, patrolling coverage, or the flossing response during infection, has not been tested. Given that infection and inflammation are well known to remodel the intestinal basement membrane, altering its stiffness and composition, this is a substantive and answerable gap rather than a merely theoretical one: the same intravital imaging approach used to characterise flossing could, in principle, be paired with genetic or pharmacological manipulation of basement-membrane stiffness to ask whether the mechanical channel matters as much as the chemical one.

$\gamma\delta$ T cells at barrier tissues: the skin

The skin presents an even more striking case of unexamined ECM engagement, because here the resident $\gamma\delta$ T cell population is not merely present within the tissue but morphologically remodelled by it. In adult mice, $\gamma\delta$ T cells are partitioned between tissues, with the great majority, around 95%, residing in the epidermis. Almost all epidermal $\gamma\delta$ T cells in mice belong to a single, invariant population known as dendritic epidermal T cells (DETCs), so named because, unlike the rounded lymphocytes found in blood or lymph node, they extend long dendritic processes between the surrounding keratinocytes (Hu et al., 2022). These dendrites are not a passive resting morphology: they are actively maintained through continuous contact with the basal keratinocyte layer and its associated basement membrane, and DETCs use them to survey a far larger area of epithelium than their cell body alone would allow, retracting and reforming them in response to local tissue damage^[8].

This dendritic architecture is itself indirect evidence of an ECM-instructed cell shape, since the same basement membrane components, laminin and collagen among them, that Gray and colleagues showed are bound by CD49a in V δ 1 cells elsewhere in the body form the substrate against which DETC dendrites

extend and adhere^[4]. DETCs additionally rely on E-cadherin-mediated contacts with keratinocytes, a junctional, rather than purely matrix, form of adhesion that nonetheless converges on the same cytoskeletal and integrin-adjacent signalling machinery used for ECM engagement^[8]. Following injury, DETCs are among the first cells to detect the disruption, retracting their dendrites and rounding up before migrating to the wound edge, where they secrete keratinocyte growth factors and contribute directly to re-epithelialisation and wound closure^[9]. It is worth noting that the DETC system as such is a mouse-specific arrangement; human skin lacks an exact equivalent invariant population, and human cutaneous $\gamma\delta$ T cells are instead a more heterogeneous mixture of subsets that nonetheless occupy the same epidermal and dermal ECM niches and are implicated in comparable roles in skin immunity and disease^[10]. The ECM-engagement questions raised below for DETCs therefore apply, in modified form, to the human cutaneous $\gamma\delta$ compartment as well, even though the precise invariant dendritic morphology described here is a feature of the mouse model system specifically. This wound-healing role, one of the best-established functions of any $\gamma\delta$ T cell subset, is fundamentally a response to a tissue in which the ECM and the epithelium built upon it have both been physically breached, and yet the literature describing it is framed almost entirely in terms of soluble growth factor and cytokine signalling rather than in terms of how DETCs mechanically detect the loss of matrix integrity that precedes those signals.

No study has asked whether DETC dendrite retraction following injury is itself a mechanotransductive response, in the sense described by Feng and colleagues for $\alpha\beta$ T cells, to a sudden loss of substrate stiffness or continuity, as opposed to a purely chemical response to keratinocyte-derived alarmins. Nor has any study asked whether the basal keratinocyte basement membrane, which stiffens with age and in chronic inflammatory skin disease in a manner broadly analogous to the age-related increase in CD103 and CD49a expression that Gray and colleagues observed in gut V δ 1 cells, drives comparable changes in DETC integrin expression or function over the lifespan^[4]. The skin therefore offers, in principle, one of the most tractable systems in which to close the gap identified throughout this review, because DETC morphology already provides a visible, quantifiable readout of matrix engagement that has yet to be connected to the molecular mechanotransduction pathway now established in conventional T cells.

$\gamma\delta$ T cells in neuroinflammatory disease

The roles of $\gamma\delta$ T cells in neuroinflammatory disease represent an area where the absence of a defined ECM-sensing mechanism becomes clinically pressing rather than merely conceptually unsatisfying. In traumatic brain injury (TBI), $\gamma\delta$ T cells exhibit complex, opposing functions. Abou-El-Hassan and

colleagues showed that V γ 4 $\gamma\delta$ T cells infiltrate the brain and secrete interferon- γ (IFN- γ) and interleukin-17 (IL-17) to activate microglia and induce neuroinflammation, while V γ 1 $\gamma\delta$ T cells secrete transforming growth factor- β (TGF- β) to maintain microglial homeostasis and dampen TBI pathology^[11]. This striking functional dichotomy between $\gamma\delta$ T cell subsets, in which two populations bearing the same basic receptor architecture produce opposite outcomes in the same injured tissue, suggests that distinct molecular programmes govern their activation and differentiation, and raises the possibility, as yet untested, that differential ECM engagement is part of what separates them. TBI is, after all, an injury defined at the tissue level by disruption of the brain's specialised perivascular and basement-membrane ECM, and it would be surprising if the two $\gamma\delta$ subsets encountered that disrupted matrix identically.

In experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis, $\gamma\delta$ T cells show disease-related changes characterised by increased infiltration into the central nervous system (CNS) during the acute disease phase, where depletion of the $\gamma\delta$ population significantly reduces clinical severity, inflammation and demyelination, with more modest effects during the chronic phase^[12]. The factors that govern $\gamma\delta$ T cell recruitment and retention within the CNS during neuroinflammatory disease, including any ECM-dependent mechanisms of adhesion or retention, remain incompletely defined by this or subsequent work. The blood-brain barrier (BBB) represents one of the most highly specialised ECM-rich structures in the body, comprising tightly regulated basement membranes and tight-junction complexes maintained jointly by endothelial cells, pericytes and astrocytic end-feet. Yet how $\gamma\delta$ T cells navigate this barrier compared with $\alpha\beta$ T cells, and whether they employ distinct adhesion or mechanosensing mechanisms to do so, has received minimal direct investigation. Because immune cells entering the CNS both respond to the local ECM and remodel it in turn through matrix metalloproteinase (MMP) expression, the question of $\gamma\delta$ T cell-specific ECM sensing is not a peripheral detail of CNS immunology but sits close to its centre: the same basement membrane whose stiffness and composition are known to gate leukocyte entry more generally has never been examined specifically for its effect on V γ 4 versus V γ 1 trafficking, despite the sharply opposing roles these two subsets play once inside the tissue.

$\gamma\delta$ T cells in the tumour microenvironment

In malignant disease, the implications of an incomplete understanding of $\gamma\delta$ T cell ECM sensing are, if anything, more pressing still, because they bear directly on a therapy already being tested in patients. $\gamma\delta$ T cells demonstrate strong cytotoxicity against diverse cancer cell types in an MHC-independent manner,

which has made them attractive candidates for adoptive cell therapy and other forms of cancer immunotherapy; however, their therapeutic efficacy in solid tumours remains inconsistent, in large part because of the immunosuppressive tumour microenvironment (TME) that surrounds most solid cancers^[3]. A substantial part of that immunosuppression is mechanical and architectural rather than purely biochemical. Solid tumours characteristically develop a dense, cross-linked collagen network, stiffened by the same LOX-family enzymes discussed above in the context of inflamed skin, which creates a physical barrier that limits immune cell infiltration and favours immune evasion^[2].

The tumour ECM is not simply denser but also biochemically altered in ways that actively reprogramme the immune infiltrate. Tarantola and colleagues showed that glycan modifications to the ECM in triple-negative breast cancer shape the innate and adaptive immune microenvironment, and that enzymatic modification of these tumour ECM glycans reprogrammes tumour-associated myeloid cells and improves conventional T cell infiltration and function^[13]. Whether $\gamma\delta$ T cells respond in the same way to this class of ECM modification, whether they are equally excluded by dense collagen and equally rescued by glycan-editing strategies, or whether their distinct integrin repertoire and, potentially, their distinct mechanotransduction machinery give them an inherent advantage or disadvantage in penetrating such a matrix, is not addressed anywhere in this literature. $\gamma\delta$ T cells are increasingly being evaluated as cellular immunotherapy candidates, including in early-phase clinical trials of adoptively transferred and engineered $\gamma\delta$ T cell products, but the rational design of $\gamma\delta$ T cells with enhanced capacity to infiltrate stiff, glycan-altered tumour matrices is presently constrained by the fact that no one has established whether $\gamma\delta$ T cells possess the integrin-actin-YAP mechanotransduction axis that Feng and colleagues mapped in $\alpha\beta$ T cells, still less whether that axis could be tuned^{[5][3]}. Closing this gap would not only complete the basic biological picture but would also identify a concrete engineering target, analogous to co-stimulatory domain selection in CAR T cell design, for improving $\gamma\delta$ T cell persistence and function inside mechanically hostile tumours. This is particularly relevant given that most current $\gamma\delta$ T cell immunotherapy platforms expand and infuse the circulating V γ 9V δ 2 subset^[3], the population least likely, on the tissue-residency logic outlined earlier in this review, to have evolved a dedicated ECM mechanosensing programme; if tissue-resident V δ 1 cells prove to possess a more robust integrin-actin-YAP axis than V γ 9V δ 2 cells, this would argue for a shift in cell-product selection, and not only in matrix-engineering strategy, for solid-tumour indications.

The central gap

Drawing the preceding sections together, a consistent pattern emerges. $\gamma\delta$ T cells are known, in exact molecular detail in some cases, to physically contact the ECM: they express CD103 and CD49a, which bind E-cadherin and collagen respectively, with expression that rises with age and with tissue-specific patterns that mirror where $\gamma\delta$ subsets reside^[4]. They are known, again in considerable behavioural detail, to alter their movement, morphology and function in response to changes in their local tissue environment, whether that is dietary composition and epithelial IL-22 signalling in the gut^[6], microbiota-dependent patrolling and infection-triggered flossing in the intestinal epithelium^[7], dendrite retraction and re-epithelialisation after skin injury^[9], opposing pro- and anti-inflammatory programmes in the injured brain^[11], or infiltration and demyelination in the inflamed spinal cord^[12]. And it is known, from work entirely outside the $\gamma\delta$ field, that $\alpha\beta$ T cells convert physical contact with a stiff ECM into a defined intracellular signal, integrin engagement driving actin polymerisation, nuclear deformation, YAP nuclear translocation and IL-2-dependent activation, through a pathway that does not depend on the T cell receptor at all^[5].

What has never been assembled is the middle term connecting these three bodies of evidence: a demonstration that $\gamma\delta$ T cell integrin engagement with the ECM feeds into any defined intracellular signalling cascade, mechanotransductive or otherwise, that shapes the behaviours described above. Every functional readout reviewed here, patrolling speed, flossing, dendrite morphology, cytokine polarisation, tumour infiltration, has been attributed either to soluble mediators (cytokines, growth factors, alarmins) or to TCR-dependent antigen recognition, and in every case the possibility that direct, TCR-independent mechanical sensing of the ECM also contributes has simply not been tested. This is not a minor gap in an otherwise complete picture; because $\gamma\delta$ T cells are disproportionately concentrated at exactly the barrier and injury sites where ECM mechanics vary most dramatically and most rapidly, over hours in infection, over years in ageing, over the course of tumour growth, a mechanosensing pathway of the kind mapped in $\alpha\beta$ T cells would be expected to matter more, not less, for this lineage.

The gap is also asymmetric in an instructive way. On one side sits a mature, mechanistic literature built almost entirely in $\alpha\beta$ T cells and non-immune cell types, in which the molecular players, integrins, F-actin, the nuclear envelope, YAP, are named and their causal order established through direct pharmacological intervention^{[5][1]}. On the other side sits an equally mature, but entirely descriptive, literature on $\gamma\delta$ T cell behaviour at barrier tissues, rich in quantified phenotypes, patrol speed, coverage

area, dendrite number, cytokine ratio, but silent on mechanism where mechanism might plausibly be mechanical rather than purely chemical^{[7][9][11]}. The two literatures have simply never been brought into contact with one another, not because anyone has tested the connection and found it absent, but because the cell populations, model systems and experimental traditions of mechanobiology on one side and $\gamma\delta$ T cell immunology on the other have developed largely in parallel. Recognising this as a gap of coordination as much as a gap of data is itself useful, because it suggests that closing it may require comparatively modest new experiments, of the kind outlined in the following section, applying existing mechanobiology tools to existing $\gamma\delta$ T cell model systems, rather than the development of wholly new methodology.

Future directions

Several concrete lines of investigation follow directly from the gap identified above. The most immediate is to test whether the integrin-actin-YAP-IL-2 axis described by Feng and colleagues in $\alpha\beta$ T cells is present, absent, or modified in $\gamma\delta$ T cell subsets, using the same engineered substrates of defined stiffness, the same pharmacological tools (cytochalasin D and blebbistatin), and the same YAP-nuclear-translocation readouts, applied specifically to sorted V δ 1, V δ 2 and DETC populations rather than to bulk T cells. Because V δ 1 cells already express CD49a and CD103 at levels that vary by tissue and age^[4], this comparison could additionally ask whether integrin expression level predicts the strength of any mechanotransductive response, giving a testable, quantitative link between the adhesion phenotype that is already well described and the signalling phenotype that is not.

A second line of investigation would extend the elegant intravital imaging methods already used to characterise gut $\gamma\delta$ IEL patrolling and flossing^[7] by pairing them with pharmacological or genetic manipulation of basement-membrane stiffness or cross-linking, for instance through LOX inhibition, to ask whether patrolling coverage, patrol speed, or the flossing response to infection are mechanically as well as chemically gated. The same logic applies with particular force to the skin, where DETC dendrite morphology already provides a visible, quantifiable proxy for matrix engagement^[8]; live imaging of dendrite dynamics on substrates of controlled stiffness, before and after simulated injury, would directly test whether dendrite retraction is a mechanotransductive event rather than a purely cytokine-driven one.

Third, single-cell and spatial transcriptomic approaches applied across tissues, of the kind Gray and colleagues have already begun to apply to human $\gamma\delta$ T cells^[4], could be mined specifically for mechanosensor and mechanotransduction-pathway gene expression, including Piezo1 and downstream YAP target genes, to generate hypotheses about which $\gamma\delta$ subsets are most likely to possess a functional mechanosensing axis before committing to lower-throughput functional validation. Finally, in the context of cancer immunotherapy, engineered $\gamma\delta$ T cell products could be tested directly for their capacity to infiltrate collagen-dense, in vitro tumour matrices of varying stiffness and glycan composition, of the kind described by Tarantola and colleagues^[13], both to establish baseline behaviour and to evaluate whether engineering strategies that tune the integrin-actin-YAP axis, if it is found to exist in $\gamma\delta$ T cells, improve infiltration and persistence. Taken together, these approaches would convert the conceptual gap identified in this review into a concrete, tractable experimental programme.

Conclusion

$\gamma\delta$ T cells sit, quite literally, on the extracellular matrix at almost every site where they are found in the body: gripping collagen and E-cadherin through CD49a and CD103 in the gut, extending dendrites across the keratinocyte basement membrane in the skin, crossing a basement-membrane-rich blood-brain barrier in neuroinflammatory disease, and confronting a stiffened, glycan-altered collagen network in solid tumours. What has not been established, in any of these settings, is whether that physical contact is read out through a dedicated mechanotransduction pathway of the kind now defined for conventional $\alpha\beta$ T cells, in which integrin engagement drives actin polymerisation, nuclear deformation, YAP nuclear translocation and IL-2-dependent activation independently of the T cell receptor. Closing this gap would complete a basic and long-overdue chapter in $\gamma\delta$ T cell biology, and would also supply a concrete, mechanistically grounded target for engineering $\gamma\delta$ T cell therapies capable of penetrating the mechanically hostile tissues, above all solid tumours, in which their therapeutic potential currently falls short of their promise.

References

1. ^aMiller AE, Hu P, Barker TH (2020). "Feeling Things Out: Bidirectional Signaling of the Cell-ECM Interface, Implications in the Mechanobiology of Cell Spreading, Migration, Proliferation, and Differentiation." *Adv Healthc Mater.* 9(8):1901445.

2. ^{a, b, c}Sutherland TE, Dyer DP, Allen JE (2023). "The Extracellular Matrix and the Immune System: A Mutually Dependent Relationship." *Science*. **379**(6633):eabp8964.
3. ^{a, b, c, d, e, f, g}Hu Y, Hu Q, Li Y, Lu L, Xiang Z, Yin Z, Kabelitz D, Wu Y (2023). " $\gamma\delta$ T Cells: Origin and Fate, Subsets, Diseases and Immunotherapy." *Signal Transduct Target Ther*. **8**(1):434.
4. ^{a, b, c, d, e, f, g, h}Gray JJ, Caron DP, Wells SB, Guyer R, Szabo P, Rainbow D, Ergen C, Rybkina K, Bradley MC, Matsumoto R, Pethe K (2024). "Human $\gamma\delta$ T Cells in Diverse Tissues Exhibit Site-Specific Maturation Dynamics Across the Life Span." *Sci Immunol*. **9**(96):eadn3954.
5. ^{a, b, c, d}Feng J, Zhao G, Zhao L, Geng L, Zhang S, Xu L, Liu M, Zhang G, Xu F, Lin M, Guo H (2026). "Integrin-Mediated Mechanosensing of Modeled Lymph Node Microenvironment Promotes T Cell Activation via Nuclear Deformation." *Research*. **9**:1121.
6. ^{a, b}Sullivan ZA, Khoury-Hanold W, Lim J, Smillie C, Biton M, Reis B, Zwick RK, Pope SD, Israni-Winger K, Parsa R, Philip N, Rashed S, Palm N, Wang A, Mucida D, Regev A, Medzhitov R (2021). " $\gamma\delta$ T Cells Regulate the Intestinal Response to Nutrient Sensing." *Science*. **371**(6535):eaba8310.
7. ^{a, b, c, d}Hoytema van Konijnenburg DPH, Reis BS, Pedicord VA, Farache J, Victora GD, Mucida D (2017). "Intestinal Epithelial and Intraepithelial T Cell Crosstalk Mediates a Dynamic Response to Infection." *Cell*. **171**(4):783–794.
8. ^{a, b, c}Nielsen MM, Witherden DA, Havran WL (2017). " $\gamma\delta$ T Cells in Homeostasis and Host Defence of Epithelial Barrier Tissues." *Nat Rev Immunol*. **17**(12):733–745.
9. ^{a, b, c}Hu W, Shang R, Yang J, Chen C, Liu Z, Liang G, He W, Luo G (2022). "Skin $\gamma\delta$ T Cells and Their Function in Wound Healing." *Front Immunol*. **13**:875076.
10. ^aCruz MS, Diamond A, Russell A, Jameson JM (2018). "Human $\alpha\beta$ and $\gamma\delta$ T Cells in Skin Immunity and Disease." *Front Immunol*. **9**:1304.
11. ^{a, b, c}Abou-El-Hassan H, Rezende RM, Izzy S, Gabriely G, Yahya T, Tatematsu BK, Habashy KJ, Lopes JR, de Oliveira GLV, Maghzi AH, Yin Z, Cox LM, Krishnan R, Butovsky O, Weiner HL (2023). "V γ 1 and V γ 4 Gamma-Delta T Cells Play Opposing Roles in the Immunopathology of Traumatic Brain Injury in Males." *Nat Commun*. **14**(1):4286.
12. ^{a, b}Rajan AJ, Gao YL, Raine CS, Brosnan CF (1996). "A Pathogenic Role for $\gamma\delta$ T Cells in Relapsing-Remitting Experimental Allergic Encephalomyelitis in the SJL Mouse." *J Immunol*. **157**(2):941–949.
13. ^{a, b}Tarantola L, Tyler EJ, Liu Y, Maniati E, Thornton KA, Martín-Otal C, Hanna D, Kumar R, Gauthier V, Hirani P, Ramos MB, Roth NJ, Bragg J, Puttock EH, McDermott J, Rajeeve V, Cutillas P, Maiques O, Soulier A, Correia de Sampaio P, Jones LJ, Davies DM, Maher J, Haslam SM, Läubli H, Pearce OMT (2026). "Glycosylated Extracellular Matrix Promotes $\gamma\delta$ T Cell Activation via TCR-CD28 Co-Receptor Signaling." *Cell*. **186**(1):1–15.

acellular Matrix Drives Immune Suppression by Modulating Macrophage-T Cell Crosstalk in Triple-Negative Breast Cancer." Nat Commun. 17:5008.

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